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KINDLING-INDUCED REACTIVATION OF IMMEDIATE EARLY GENES IS ASSOCIATED WITH INCREASED SEIZURE SEVERITY AND NEUROINFLAMMATION IN 5XFAD MODEL OF ALZHEIMER'S DISEASE

POSTER SESSION 07 - SECTION: ALZHEIMER'S DISEASE

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Alzheimer's disease (AD) is a neurodegenerative disease affecting 50 million people worldwide. There is increased prevalence of epilepsy in patients with AD, and the two diseases are thought to have a bi-directional association. This study aimed to understand the relationship between AD and seizure susceptibility and to characterise the molecular signature of epileptogenesis in the setting of AD. Transgenic 5xFAD mice (N=20) and WT littermates (N=22) underwent electrical amygdala kindling to induce epilepsy phenotype, or were treated as sham (electrode implantation without stimulation). Kindling rate, seizure severity and cognitive behavioural performance were compared across the kindled and sham 5xFAD and WT mice. The transcriptome (RNA-sequencing) of the hippocampal tissue was examined through differential expression analysis, followed by weighted gene coexpression network analysis (WGCNA). The 5xFAD mice showed increased susceptibility to kindling-induced seizures and had significantly longer and more severe seizures compared to WT littermates (p=0.0002). They also showed impaired spatial memory compared to WT group, as measured by the Y-maze test. Transcriptomic profiling and WGCNA identified modules of inflammatory and cellular stress-associated genes correlated with seizure severity and impaired spatial memory. Notably, a module of early immediate genes showed significant correlation with kindled-5xFAD group, but not the shams. The regulatory hub genes, pcdh8, BDNF, and Nptx2, are involved in synapse formation/maintenance in homeostatic conditions and their dysregulation leads to loss of dendritic spine density. We speculate that the inherent low expression level of these hub genes in 5xFAD may contribute to increased susceptibility to epileptogenesis and seizure-associated damage, and represent potential therapeutic targets.

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Altered metabolic pathways in a transgenic mouse model suggest mechanistic role of amyloid precursor protein overexpression in Alzheimer's disease.
The mechanistic role of amyloid precursor protein (APP) in Alzheimer's disease (AD) remains unclear.
Metabolomics, 2021; 17